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| | | |
|---|---|---|
| NEWS 1 | | Web Page URLs for STN Seminar Schedule - N. America |
| NEWS 2 | | "Ask CAS" for self-help around the clock |
| NEWS 3 | DEC 23 | New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2 |
| NEWS 4 | JAN 13 | IPC 8 searching in IFIPAT, IFIUDB, and IFICDB |
| NEWS 5 | JAN 13 | New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC |
| NEWS 6 | JAN 17 | Pre-1988 INPI data added to MARPAT |
| NEWS 7 | JAN 17 | IPC 8 in the WPI family of databases including WPIFV |
| NEWS 8 | JAN 30 | Saved answer limit increased |
| NEWS 9 | FEB 21 | STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results |
| NEWS 10 | FEB 22 | The IPC thesaurus added to additional patent databases on STN |
| NEWS 11 | FEB 22 | Updates in EPFULL; IPC 8 enhancements added |
| NEWS 12 | FEB 27 | New STN AnaVist pricing effective March 1, 2006 |
| NEWS 13 | FEB 28 | MEDLINE/LMEDLINE reload improves functionality |
| NEWS 14 | FEB 28 | TOXCENTER reloaded with enhancements |
| NEWS 15 | FEB 28 | REGISTRY/ZREGISTRY enhanced with more experimental spectral property data |
| NEWS 16 | MAR 01 | INSPEC reloaded and enhanced |
| NEWS 17 | MAR 03 | Updates in PATDPA; addition of IPC 8 data without attributes |
| NEWS 18 | MAR 08 | X.25 communication option no longer available after June 2006 |
| NEWS 19 | MAR 22 | EMBASE is now updated on a daily basis |
| NEWS 20 | APR 03 | New IPC 8 fields and IPC thesaurus added to PATDPAFULL |
| NEWS 21 | APR 03 | Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL |
| NEWS 22 | APR 04 | STN AnaVist $500 visualization usage credit offered |
| NEWS 23 | APR 12 | LINSPEC, learning database for INSPEC, reloaded and enhanced |
| NEWS 24 | APR 12 | Improved structure highlighting in FQHIT and QHIT display in MARPAT |
| NEWS 25 | APR 12 | Derwent World Patents Index to be reloaded and enhanced during second quarter; strategies may be affected |

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
http://download.cas.org/express/v8.0-Discover/

| | |
|---|---|
| NEWS HOURS | STN Operating Hours Plus Help Desk Availability |
| NEWS LOGIN | Welcome Banner and News Items |
| NEWS IPC8 | For general information regarding STN implementation of IPC 8 |

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 12:21:30 ON 23 APR 2006

=>
Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?
Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> FILE REGISTRY

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.21 | 0.21 |

FILE 'REGISTRY' ENTERED AT 12:21:42 ON 23 APR 2006
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 21 APR 2006 HIGHEST RN 881539-69-1
DICTIONARY FILE UPDATES: 21 APR 2006 HIGHEST RN 881539-69-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

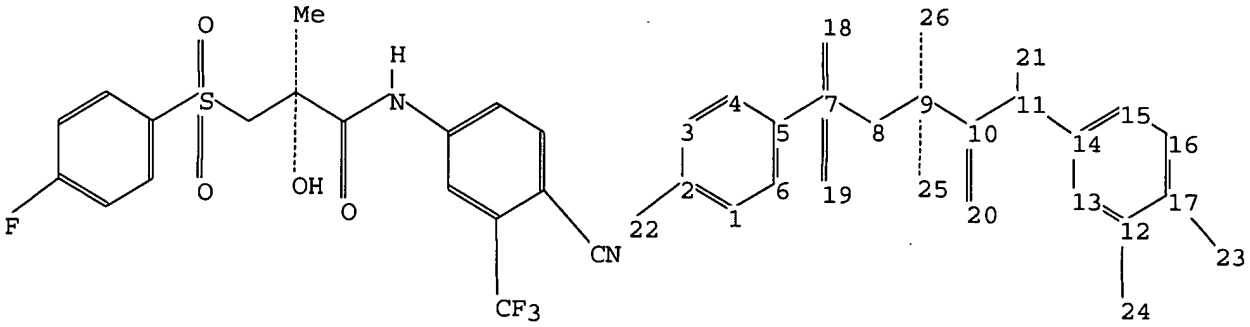
**********
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
**********

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10030665.str

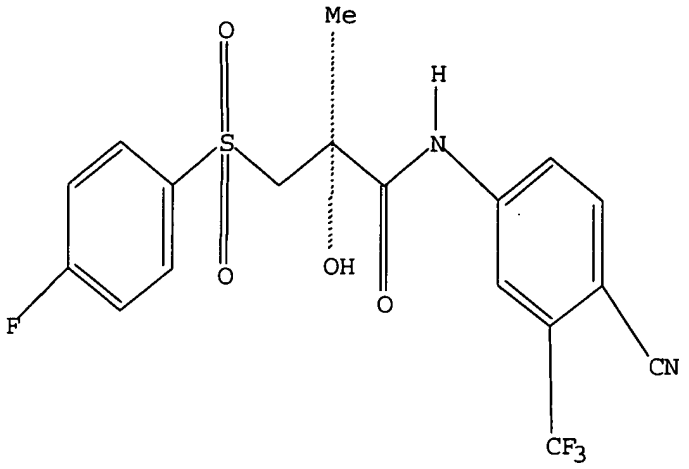



chain nodes :
7 8 9 10 11 18 19 20 21 22 23 24 25 26
ring nodes :
1 2 3 4 5 6 12 13 14 15 16 17
chain bonds :
2-22 5-7 7-8 7-18 7-19 8-9 9-10 9-25 9-26 10-11 10-20 11-14 11-21
12-24 17-23
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 12-13 12-17 13-14 14-15 15-16 16-17
exact/norm bonds :
5-7 7-8 7-18 7-19 9-25 9-26 10-11 10-20 11-14
exact bonds :
2-22 8-9 9-10 11-21 12-24 17-23
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 12-13 12-17 13-14 14-15 15-16 16-17
isolated ring systems :
containing 1 : 12 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS 10:CLASS
11:CLASS 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:CLASS
20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR




Structure attributes must be viewed using STN Express query preparation.

```
=> s l1
SAMPLE SEARCH INITIATED 12:21:59 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        1 TO ITERATE

100.0% PROCESSED         1 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            1 TO       80
PROJECTED ANSWERS:               0 TO        0

L2             0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 12:22:06 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -       44 TO ITERATE

100.0% PROCESSED        44 ITERATIONS                               7 ANSWERS
SEARCH TIME: 00.00.01

L3             7 SEA SSS FUL L1

=> FIL HCAPLUS
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     166.94     167.15

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FILE COVERS 1907 - 23 Apr 2006 VOL 144 ISS 18
FILE LAST UPDATED: 21 Apr 2006 (20060421/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s l3
L4          558 L3

=> s l4 and process
       2230567 PROCESS
       1508268 PROCESSES
       3328775 PROCESS
                 (PROCESS OR PROCESSES)
L5           37 L4 AND PROCESS

=> s l5 and thionyl chloride
         14256 THIONYL
             2 THIONYLS
         14258 THIONYL
                 (THIONYL OR THIONYLS)
       1072123 CHLORIDE
        156700 CHLORIDES
       1143870 CHLORIDE
                 (CHLORIDE OR CHLORIDES)
         13439 THIONYL CHLORIDE
                 (THIONYL(W)CHLORIDE)
L6            1 L5 AND THIONYL CHLORIDE

=> s l5 and py<=1999
      19944486 PY<=1999
L7            4 L5 AND PY<=1999

=> d l6 ibib abs hitstr tot

L6   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2005:141019  HCAPLUS
DOCUMENT NUMBER:          142:240198
TITLE:                    Process for production of
                          N-methacryloyl-4-cyano-3-trifluoromethylaniline,
                          method for stabilization of the same, and
                          process for production of bicalutamide
INVENTOR(S):              Sugi, Kiyoshi; Shintaku, Tetsuya; Katsura, Tadashi;
                          Itaya, Nobushige
PATENT ASSIGNEE(S):       Sumitomo Chemical Company, Limited, Japan
SOURCE:                   PCT Int. Appl., 28 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
```

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

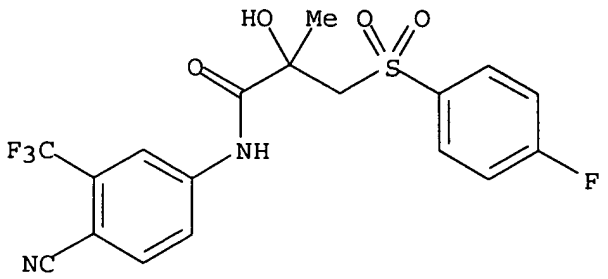
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005014531 | A1 | 20050217 | WO 2004-JP11800 | 20040811 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| JP 2005060302 | A2 | 20050310 | JP 2003-292498 | 20030812 |
| PRIORITY APPLN. INFO.: | | | JP 2003-292498 A | 20030812 |

OTHER SOURCE(S): CASREACT 142:240198

AB A **process** for the production of N-methacryloyl-4-cyano-3-trifluoromethylaniline comprises reacting 4-cyano-3-trifluoromethylaniline with methacrylic acid or a reactive derivative thereof in the presence of a polymerization inhibitor; a **process** for the production of bicalutamide comprises reacting 4-cyano-3-trifluoromethylaniline with methacrylic acid or a reactive derivative thereof in the presence of a polymerization inhibitor and reacting the obtained N-methacryloyl-4-cyano-3-trifluoromethylaniline with a peroxycarboxylic acid, 4-fluorothiophenol, and a peroxycarboxylic acid successively; and a method for the stabilization of N-methacryloyl-4-cyano-3-trifluoromethylaniline comprises incorporating a polymerization inhibitor into N-methacryloyl-4-cyano-3-trifluoromethylaniline. Thus, treatment of methacrylic acid in DMF with **thionyl chloride** in the presence of 2,6-di-tert-butyl-4-methylphenol (polymerization inhibitor), followed by reaction with 4-cyano-3-trifluoromethylaniline, gave N-methacryloyl-4-cyano-3-trifluoromethylaniline in 89% yield.

IT **90357-06-5P**, Bicalutamide
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**process** for production of N-methacryloyl-4-cyano-3-trifluoromethylaniline by reaction of 4-cyano-3-trifluoromethylaniline with methacrylic acid derivative method for stabilization of said aniline derivative and **process** for production of bicalutamide)

RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l7 ibib abs hitstr tot

L7 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:92156 HCAPLUS
DOCUMENT NUMBER: 133:3008
TITLE: Prostate cancer: molecular biology of early progression to androgen independence
AUTHOR(S): Sadar, M. D.; Hussain, M.; Bruchovsky, N.
CORPORATE SOURCE: British Columbia Cancer Agency, Department of Cancer Endocrinology, Vancouver, BC, V5Z 4E6, Can.
SOURCE: Endocrine-Related Cancer (**1999**), 6(4), 487-502
CODEN: ERCAE9; ISSN: 1351-0088
PUBLISHER: Society for Endocrinology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

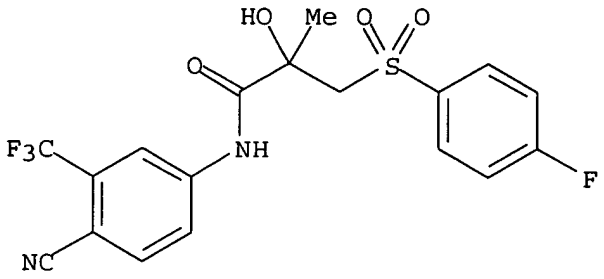
AB A review, with 109 refs. To improve the therapy for prostate cancer, it will be necessary to address the problems of progression to androgen independence and the **process** of metastatic spread of tumor. The complexity of the latter condition is likely to mitigate against the immediate development of relevant therapeutic approaches. However, the basis of androgen independence appears to be a problem of simpler dimensions and more amenable to treatment with current therapeutic technol. Since early tumor progression can be detected by an incomplete prostate-specific antigen (PSA) response to androgen withdrawal therapy, a study of the mol. biol. of PSA gene regulation may well provide insight into new methods for preventing or delaying this problem. Mounting evidence suggests that ligand-independent activation of the androgen receptor may be one underlying mechanism of androgen independence. In the absence of androgen, a compensatory increase in the activity of cAMP-dependent protein kinase (PKA) enhances the ability of the androgen receptor to bind to the response elements regulating PSA gene expression. The activation of the androgen receptor through upregulation of the PKA signal transduction pathway involves the amino-terminus of the androgen receptor, the function of which may be altered either by modifications such as phosphorylation, or through interactions with co-regulators or other proteins. Of therapeutic interest is the fact that this effect can be counteracted exptl. by the anti-androgen, bicalutamide, and clin. by several other similar agents. We speculate that the inhibition of PKA-activated androgen receptor might also be accomplished by decoy mols. that can bind to the relevant activated site on the amino-terminus or competitively interact with proteins recruited by the PKA pathway that are

responsible for activating the receptor in the absence of androgen. Such mols. might include small mimetic substances or agents that can gain access to the nucleus of the cell.

IT **90357-06-5**, Bicalutamide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prostate cancer mol. biol. of early progression to androgen independence)

RN 90357-06-5 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 109 THERE ARE 109 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:743995 HCAPLUS
DOCUMENT NUMBER: 130:134291
TITLE: Neoadjuvant hormone therapy before surgery for prostate cancer: the Italian experience (PROSIT study)
AUTHOR(S): Pagano, F.; Bono, A.; Zattoni, F.; Montironi, R.; Galetti, T. Prayer
CORPORATE SOURCE: The Prosit Study Group, Department of Urology, University of Padova, Italy
SOURCE: Molecular Urology (**1998**), 2(3), 189-194
CODEN: MOURFE; ISSN: 1091-5362
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

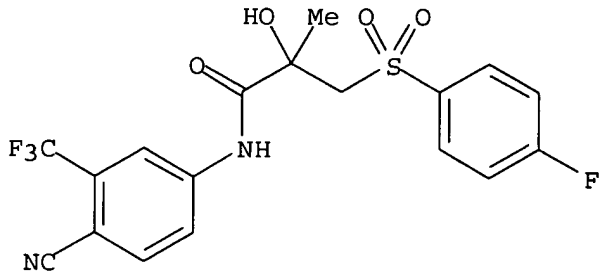
AB Despite the growing use in clin. practice of neoadjuvant hormone therapy (NHT) for patients with clin. localized prostate cancer eligible for radical retropubic prostatectomy (RRP), to the authors' knowledge, no randomized trial has addressed the issue of NHT for 6 mo compared with 3 mo and a control arm. It seems worthwhile to determine NHT efficacy in a randomized multicenter trial, testing the efficacy of total androgen blockade (TAB) for 3 or 6 mo in patients with clin. localized prostate cancer (Stage B [AUS/T2N0M0; UICC 1992] or State C [T3N0M0]) eligible for radical retropubic prostatectomy 238 patients had been enrolled, and following the randomization **process**, 82 patients were included in the immediate-surgery arm (Surgery), 77 in the 12-wk NHT arm (12 NHT), and 79 in the 24-wk NHT arm (24 NHT). In both of the NHT treatment arms, there was a trend to a reduction of clin. understaging in clin. Stage B tumors and an increase of clin. overstaging in clin. Stage C tumors. When primary Gleason grade was compared with the final grade in the treated

tumors, there was an apparent higher grade in the surgical than the biopsy specimens. Preliminary results show a better effect of NHT on Stage B tumors.

IT **90357-06-5**, Bicalutamide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoadjuvant hormone therapy before surgery for prostate cancer in humans)

RN 90357-06-5 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:950238 HCAPLUS

DOCUMENT NUMBER: 123:330228

TITLE: Ligand-induced conformational alterations of the androgen receptor analyzed by limited trypsinization. Studies on the mechanism of antiandrogen action

AUTHOR(S): Kuil, Cor W.; Berrevoets, Cor A.; Mulder, Eppo

CORPORATE SOURCE: Dep. Endocrinol. Reproduction, Erasmus Univ. Rotterdam, Rotterdam, 3000 DR, Neth.

SOURCE: Journal of Biological Chemistry (1995), 270(46), 27569-76
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

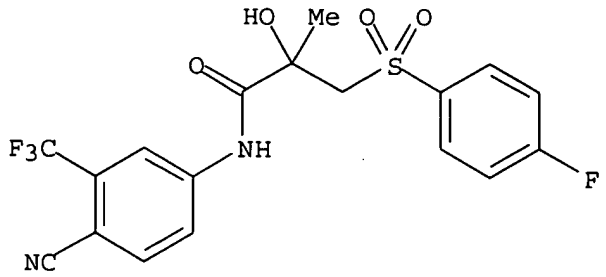
AB Limited proteolysis of in vitro produced human androgen receptor was used to probe the different conformations of the receptor after binding of androgens and several antiandrogens. The results provide evidence for five different conformations of the receptor, as detected by the formation of proteolysis resisting fragments: (1) an initial conformation of the unoccupied receptor not resisting proteolytic attack; and receptor conformations characterized by (2) a 35-kDa proteolysis resisting fragment spanning the ligand binding domain and part of the hinge region, obtained with most antagonists, and in an initial step after agonist binding; (3) a 29-kDa proteolysis resisting fragment spanning the ligand binding domain, obtained in the presence of agonists after an activation **process**; (4) and (5) 30- and 25-kDa fragments, derived from 2 and 3, but missing part of the C terminus, obtained with RU 486 (RU 486 has antiandrogenic properties, besides its effects as an antiprogestagen/antiglucocorticoid).

Concomitantly with the change from 2 to 3 (and of 4 to 5 for RU 486), dissociation of the 8 S complex of receptor with associated proteins occurred. With a mutant receptor (LNCaP cell mutation in C-terminal region), some antagonists activated transcription analogous to agonists, and induced the activated receptor conformation 3. A mutant lacking the C-terminal 12 amino acids bound RU 486 but not androgens, and formed with RU 486 conformation 5. These data imply that, after the initial rapid binding of ligand, androgens induce a conformational change of the receptor, a **process** that also involves release of associated proteins. RU 486 induces an inappropriate conformation of the C-terminal end, similar as found for its effect on the progesterone receptor. In contrast, the other antiandrogens act at a different step in the mechanism of action: they do not induce an abnormal conformation, but act earlier and prevent a conformation change by stabilizing a complex with associated proteins.

IT **90357-06-5**, ICI 176334
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(antiandrogen mechanism of action in relation to ligand-induced androgen receptor conformational alterations)

RN 90357-06-5 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)




L7 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1992:99546 HCAPLUS

DOCUMENT NUMBER: 116:99546

TITLE: Anti-androgens and the mutated androgen receptor of LNCaP cells: differential effects on binding affinity, heat-shock protein interaction, and transcription activation

AUTHOR(S): Veldscholte, Jos; Berrevoets, Cor A.; Brinkmann, Albert O.; Grootegoed, J. Anton; Mulder, Eppo

CORPORATE SOURCE: Dep. Endocrinol. Reprod., Erasmus Univ., Rottendam, 3000 DR, Neth.

SOURCE: Biochemistry (**1992**), 31(8), 2393-9
CODEN: BICHAW; ISSN: 0006-2960

DOCUMENT TYPE: Journal

LANGUAGE: English

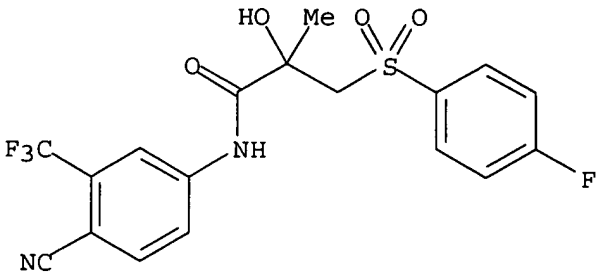
AB Previous studies have shown that LNCaP prostate tumor cells contain an androgen receptor (AR) with a point mutation in the steroid-binding domain (codon 868, Thr to Ala). This defect leads to a change in specificity of the AR. Estrogens, progestagens, and some antiandrogens (e.g., cyproterone acetate, hydroxyflutamide, nilutamide) stimulate LNCaP cell growth rate through the AR. The present studies indicate, that not all

antiandrogens showed agonistic effects with the mutated receptor. The growth rate of LNCaP cells did not increase with the antiandrogen ICI 176,334, nor could this compound increase transcription activation of the reporter gene construct via the mutant receptor in a cotransfection system [HeLa cell cotransfection system with an androgen-regulated reporter gene construct (pG29G-tk-CAT) and the mutant receptor as trans-vector]. Interaction of the AR of LNCaP cells with heat-shock proteins was studied by isolation of the receptor with a specific monoclonal antibody and characterization of associated proteins. Hsp90, hsp70, and hsp56 copptd. with the AR. Incubation of the cells at 37° with androgen (R 1881, 10 nM) or the antiandrogen hydroxyflutamide, prior to receptor isolation, resulted in dissociation of the AR-heat-shock protein complex. This dissociation is paralleled by the transformation to a tight nuclear-binding form of the AR. In contrast, ICI 176,334 could not induce a release of heat-shock proteins and did not increase nuclear binding, but inhibited the transformation **process** induced by R 1881. A mechanism of action of antiandrogens in LNCaP cells is proposed in which these compds. affect different steps in the **processes** of receptor transformation and transcription activation. In LNCaP cells, ICI 176,334 shows decreased affinity for the AR and affects steps before DNA binding occurs. In contrast, other antiandrogens including hydroxyflutamide show increased affinity for the mutant AR, affect receptor transformation to the DNA-binding state, and permit interaction of the receptor with the transcription machinery.

IT **90357-06-5**, ICI 176334
RL: PRP (Properties)
(antiandrogen action mechanism of, in prostate tumor cells, receptor transformation and transcription activation in relation to)

RN 90357-06-5 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)




=> FIL REGISTRY

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 60.97 | 228.12 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -3.75 | -3.75 |

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 21 APR 2006 HIGHEST RN 881539-69-1
DICTIONARY FILE UPDATES: 21 APR 2006 HIGHEST RN 881539-69-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

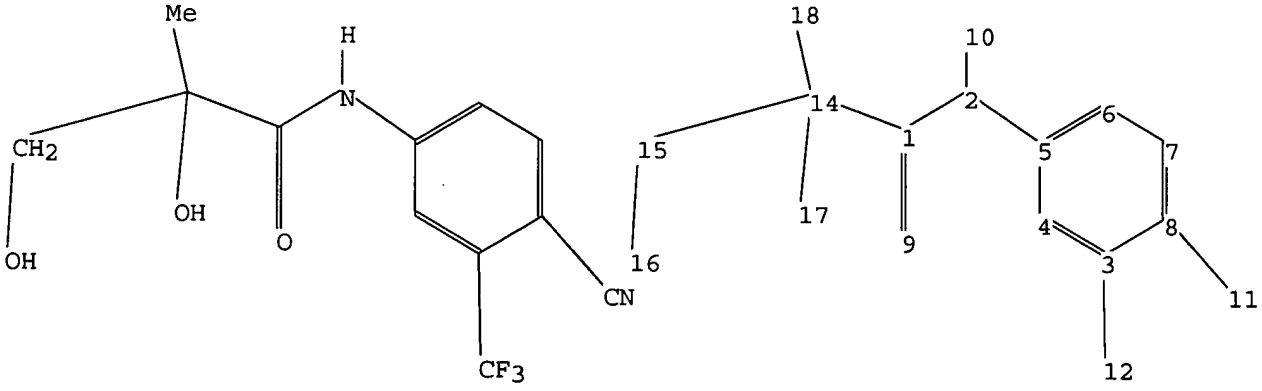
**********
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
**********

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10030665a.str



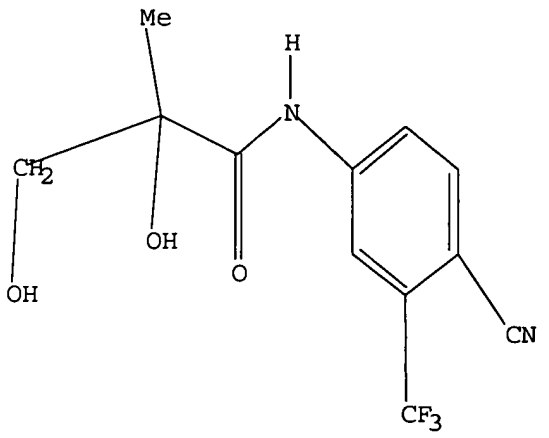

chain nodes :
1 2 9 10 11 12 14 15 16 17 18
ring nodes :
3 4 5 6 7 8
chain bonds :
1-9 1-2 1-14 2-5 2-10 3-12 8-11 14-15 14-17 14-18 15-16
ring bonds :

3-4 3-8 4-5 5-6 6-7 7-8
exact/norm bonds :
1-9 1-2 2-5 14-17
exact bonds :
1-14 2-10 3-12 8-11 14-15 14-18 15-16
normalized bonds :
3-4 3-8 4-5 5-6 6-7 7-8
isolated ring systems :
containing 3 :

Match level :
1:CLASS 2:CLASS 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:CLASS 10:CLASS
11:CLASS 12:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS

L8 STRUCTURE UPLOADED

=> d l8
L8 HAS NO ANSWERS
L8 STR




Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED - 11 TO ITERATE

100.0% PROCESSED 11 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 22 TO 418
PROJECTED ANSWERS: 0 TO 0

L9 0 SEA SSS SAM L8

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=> s l8 sss full
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FULL SCREEN SEARCH COMPLETED -      283 TO ITERATE

100.0% PROCESSED      283 ITERATIONS                          3 ANSWERS
SEARCH TIME: 00.00.01

L10           3 SEA SSS FUL L8

=> FIL HCAPLUS
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   166.94     395.06

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00      -3.75

FILE 'HCAPLUS' ENTERED AT 12:30:59 ON 23 APR 2006
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FILE COVERS 1907 - 23 Apr 2006  VOL 144 ISS 18
FILE LAST UPDATED: 21 Apr 2006  (20060421/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s l10
L11           5 L10
=> d his

     (FILE 'HOME' ENTERED AT 12:21:30 ON 23 APR 2006)

     FILE 'REGISTRY' ENTERED AT 12:21:42 ON 23 APR 2006
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L3             7 S L1 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 12:22:12 ON 23 APR 2006
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L5            37 S L4 AND PROCESS
L6             1 S L5 AND THIONYL CHLORIDE
L7             4 S L5 AND PY<=1999
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L8 STRUCTURE UPLOADED
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L10 3 S L8 SSS FULL

FILE 'HCAPLUS' ENTERED AT 12:30:59 ON 23 APR 2006
L11 5 S L10

=> s l4 and l11
L12 5 L4 AND L11

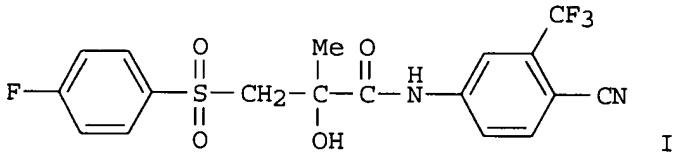
=> s l5 and l11
L13 3 L5 AND L11

=> d l13 ibib abs hitstr tot

L13 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:293441 HCAPLUS
DOCUMENT NUMBER: 140:303414
TITLE: **Process** for making bicalutamide and intermediates thereof
INVENTOR(S): Thijs, Lambertus; Keltjens, Rolf; Ettema, Gerrit J. B.
PATENT ASSIGNEE(S): Neth.
SOURCE: U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S. Ser. No. 261,492.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2004068135 | A1 | 20040408 | US 2003-682530 | 20031010 |
| US 2003073742 | A1 | 20030417 | US 2002-261492 | 20021002 |
| US 6818766 | B2 | 20041116 | | |

PRIORITY APPLN. INFO.: US 2002-261492 A2 20021002
OTHER SOURCE(S): MARPAT 140:303414
GI

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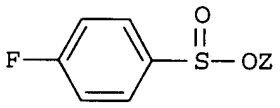


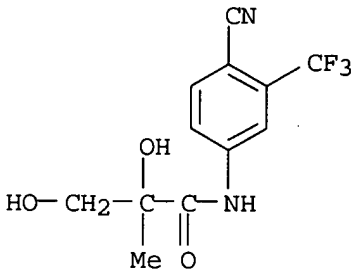

II

AB Bicalutamide (I) and/or its intermediates are made by reaction of p-fluorobenzenesulfinic acid salt (II; Z = a cation) with 2-hydroxyisobutyric acid derivs. of formula YCH2C(Me)(OX)COA (A = OR;

wherein R = H, C1-6 alkyl, C3-6 cycloalkyl, Ph, benzyl,4-cyano-3-trifluoromethylanilino; Y = leaving group and X = H; or X and Y are joined together to form a 3- to 6-membered heterocyclic ring, in particular oxirane ring; or X and A are joined together to form a 5- to 10-membered fused or unfused heterocyclic ring with the proviso that if a ring nitrogen is present, it may be substituted by a 3-trifluoromethyl-4-cyanophenyl group), YCH2CMe:CH2 (Y = same as above), or YCH2COMe (Y = same as above). Thus, 0.500 g N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-2-oxiranecarboxamide (III) was dissolved in dissolved in a mixture of 40 mL CHCl3 and 40 mL H2O, successively treated with 371 mg sodium p-fluorobenzenesulfinate and 298 mg tetrabutylammonium bromide, and refluxed for 96 h to give, after workup and silica gel chromatog., 380 mg I (48% yield). Similarly, chiral (R)-I was obtained using chiral epoxide (S)-III in 43% yield.

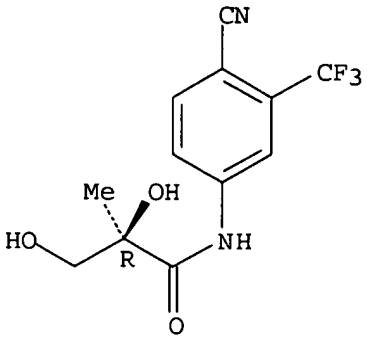
IT **316373-92-9P**, N-[4-Cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methylpropanamide **316373-93-0P**, N-[4-Cyano-3-(trifluoromethyl)phenyl]-(2R)-2,3-dihydroxy-2-methylpropanamide **316373-94-1P**, (2S)-N-[4-Cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methylpropanamide
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of bicalutamide by coupling of N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-2-orixanecarboxamide or -3-(halo or mesyloxy)-2-hydroxy-2-methylpropanamide with sodium p-fluorobenzenesulfinate)

RN 316373-92-9 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl- (9CI) (CA INDEX NAME)



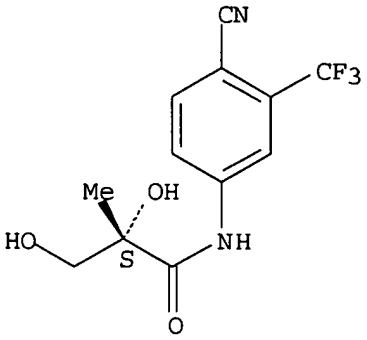

RN 316373-93-0 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

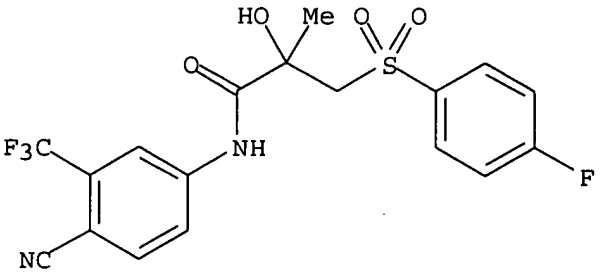


RN 316373-94-1 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



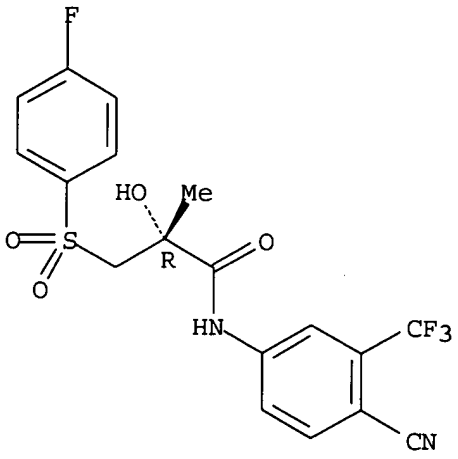
IT **90357-06-5P**, Bicalutamide **113299-40-4P**, (R)-Bicalutamide
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of bicalutamide by coupling of N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-2-orixanecarboxamide or -3-(halo or mesyloxy)-2-hydroxy-2-methylpropanamide with sodium p-fluorobenzenesulfinate)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



RN 113299-40-4 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




L13 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:511288 HCAPLUS
DOCUMENT NUMBER: 139:85122
TITLE: **Process** for preparing bicalutamide and crystals thereof
INVENTOR(S): Shintaku, Tetsuya; Katsura, Tadashi; Itaya, Nobushige
PATENT ASSIGNEE(S): Sumika Fine Chemicals Co., Ltd., Japan
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003053920 | A1 | 20030703 | WO 2002-JP13058 | 20021213 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2469594 | AA | 20030703 | CA 2002-2469594 | 20021213 |
| AU 2002354475 | A1 | 20030709 | AU 2002-354475 | 20021213 |
| EP 1462442 | A1 | 20040929 | EP 2002-788815 | 20021213 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| BR 2002014933 | A | 20041214 | BR 2002-14933 | 20021213 |
| US 2003191337 | A1 | 20031009 | US 2003-362410 | 20030224 |
| US 6740770 | B2 | 20040525 | | |

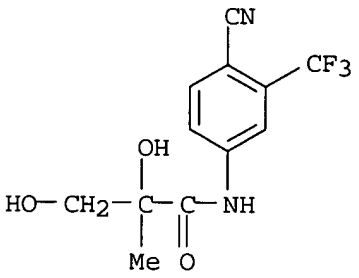
| | | | | |
|---|---|---|---|---|
| US 2004133031 | A1 | 20040708 | US 2003-740140 | 20031218 |
| ZA 2004004891 | A | 20050621 | ZA 2004-4891 | 20040621 |
| PRIORITY APPLN. INFO.: | | | JP 2001-380686 | A 20011213 |
| | | | JP 2002-166213 | A 20020606 |
| | | | WO 2002-JP13058 | W 20021213 |
| | | | US 2003-362410 | A3 20030224 |

AB The invention relates to crystals of bicalutamide having a specific crystal form, and industrially practicable **processes** for the production of bicalutamide and crystals thereof; these **processes** are excellent in environmental friendliness and economical efficiency. Bicalutamide was prepared by epoxidn. of N-methacryloyl-4-cyano-3-trifluoromethylaniline, followed by reaction with 4-fluorothiophenol, and oxidation

IT **316373-92-9P**
RL: BYP (Byproduct); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(preparation of bicalutamide in multi-step **process** starting from N-methacryloyl-4-cyano-3-trifluoromethylaniline and **process** for production of crystals of bicalutamide)

RN 316373-92-9 HCAPLUS

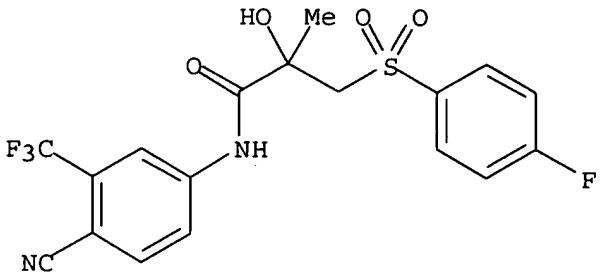
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl- (9CI) (CA INDEX NAME)




IT **90357-06-5P**, Bicalutamide
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of bicalutamide in multi-step **process** starting from N-methacryloyl-4-cyano-3-trifluoromethylaniline and **process** for production of crystals of bicalutamide)

RN 90357-06-5 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:300625 HCAPLUS
DOCUMENT NUMBER: 138:321017
TITLE: **Process** for making bicalutamide using a p-fluorobenzenesulfinic acid salt.
INVENTOR(S): Thijs, Lambertus; Keltjens, Rolf; Ettema, Gerrit Jan Bouke
PATENT ASSIGNEE(S): Synthon B.V., Neth.
SOURCE: U.S. Pat. Appl. Publ., 24 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003073742 | A1 | 20030417 | US 2002-261492 | 20021002 |
| US 6818766 | B2 | 20041116 | | |
| WO 2004031136 | A1 | 20040415 | WO 2003-EP11166 | 20031001 |
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| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003273965 | A1 | 20040423 | AU 2003-273965 | 20031001 |
| EP 1546093 | A1 | 20050629 | EP 2003-757932 | 20031001 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| US 2004068135 | A1 | 20040408 | US 2003-682530 | 20031010 |
| PRIORITY APPLN. INFO.: | | | US 2002-261492 A | 20021002 |
| | | | WO 2003-EP11166 W | 20031001 |

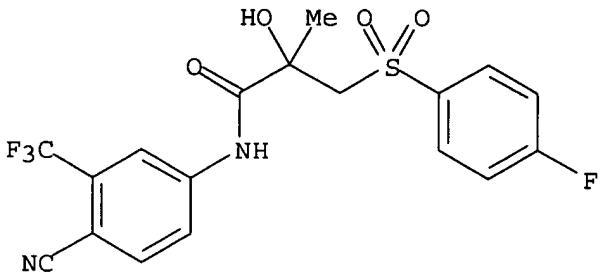
OTHER SOURCE(S): CASREACT 138:321017; MARPAT 138:321017

AB Title **process** is claimed. Thus, N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-2-oxiranecarboxamide (preparation given), Na p-fluorobenzenesulfinate, and Bu4NBr were refluxed together for 96 h to give 48% bicalutamide.

IT **90357-06-5P**, Bicalutamide **113299-40-4P**

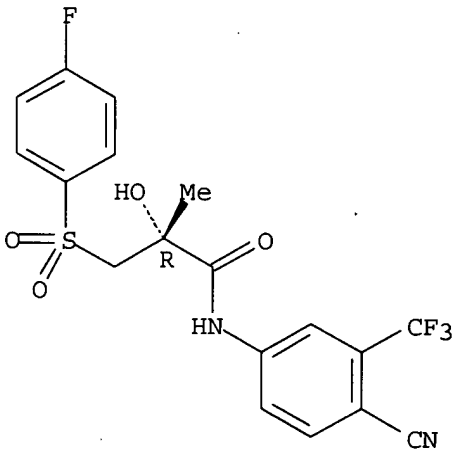
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(**process** for making bicalutamide using a p-fluorobenzenesulfinic acid salt)

RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



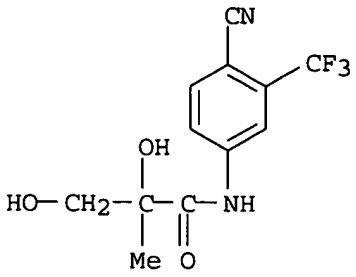

RN 113299-40-4 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



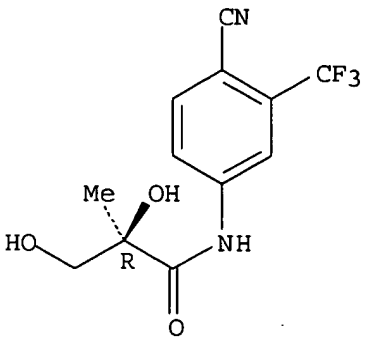

IT **316373-92-9P 316373-93-0P 316373-94-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**process** for making bicalutamide using a p-fluorobenzenesulfinic acid salt)

RN 316373-92-9 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl- (9CI) (CA INDEX NAME)



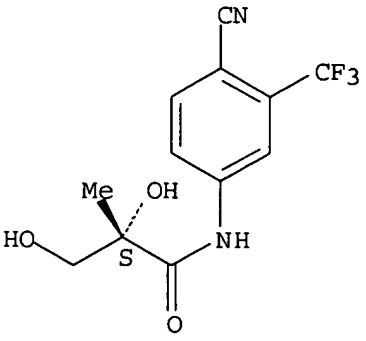
RN 316373-93-0 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 316373-94-1 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

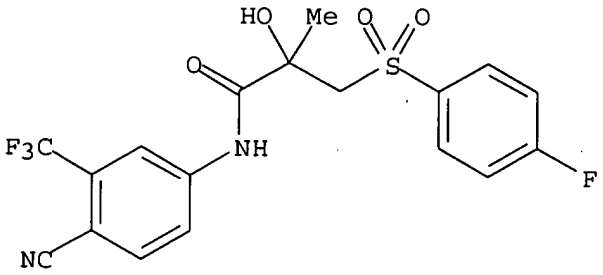
=> d l12 ibib abs hitstr tot

L12 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1274892 HCAPLUS
DOCUMENT NUMBER: 144:199095
TITLE: High-performance liquid chromatographic enantioseparation of bicalutamide and its related compounds
AUTHOR(S): Toeroek, Roland; Bor, Adam; Orosz, Gyoergy; Lukacs, Ferenc; Armstrong, Daniel W.; Peter, Antal
CORPORATE SOURCE: Department of Inorganic and Analytical Chemistry, University of Szeged, Szeged, H-6720, Hung.
SOURCE: Journal of Chromatography, A (2005), 1098(1-2), 75-81
CODEN: JCRAEY; ISSN: 0021-9673
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

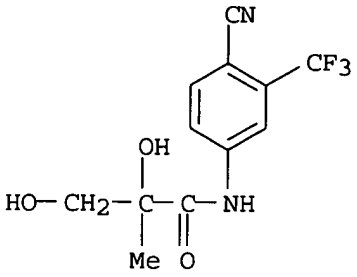
AB Direct high-performance liquid chromatog. methods were developed for the enantiosepn. of (R,S)-bicalutamide (1) and its analogs (±)-3-chloro-N-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropanamide (2), (±)-N-(4-cyano-3-(trifluoro-methyl)phenyl)-2-methyloxirane-2-carboxamide (3), (±)-4-fluorophenylsulfonyl-2-hydroxy-2-methylpropionic acid (4), and (±)-3-hydroxy-N-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropanamide (5). The methods involved the use of a cellulose-based Chiralcel OD-H, macrocyclic glycopeptide-based Chirobiotic T, TAG and R, β-cyclodextrin-based Cyclobond I 2000SN, and t-Bu carbamate-derivatized quinine-based columns. The conditions affording the best resolution were found by selection and variation of the mobile-phase compns., and the differences in separation capability of the methods were noted. The sequence of elution of the enantiomers was determined in all cases.

IT **90357-06-5**, Bicalutamide **316373-92-9**
RL: ANT (Analyte); ANST (Analytical study)
(HPLC enantiosepn. of bicalutamide and its related compds.)

RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)

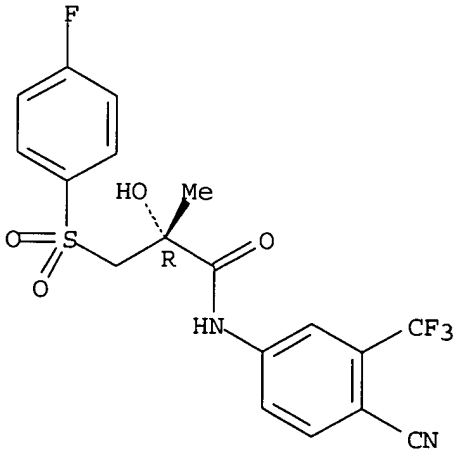



RN 316373-92-9 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl- (9CI) (CA INDEX NAME)



IT **113299-40-4**, (R)-Bicalutamide
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(HPLC enantiosepn. of bicalutamide and its related compds.)
RN 113299-40-4 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

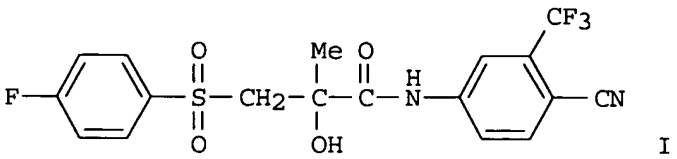


REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

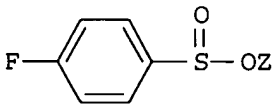
L12 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:293441 HCAPLUS
DOCUMENT NUMBER: 140:303414
TITLE: Process for making bicalutamide and intermediates thereof
INVENTOR(S): Thijs, Lambertus; Keltjens, Rolf; Ettema, Gerrit J. B.
PATENT ASSIGNEE(S): Neth.
SOURCE: U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S. Ser. No. 261,492.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2004068135 | A1 | 20040408 | US 2003-682530 | 20031010 |
| US 2003073742 | A1 | 20030417 | US 2002-261492 | 20021002 |
| US 6818766 | B2 | 20041116 | | |

PRIORITY APPLN. INFO.: US 2002-261492 A2 20021002
OTHER SOURCE(S): MARPAT 140:303414
GI



I

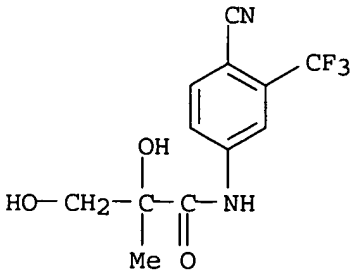


II

AB Bicalutamide (I) and/or its intermediates are made by reaction of p-fluorobenzenesulfinic acid salt (II; Z = a cation) with 2-hydroxyisobutyric acid derivs. of formula YCH2C(Me)(OX)COA (A = OR; wherein R = H, C1-6 alkyl, C3-6 cycloalkyl, Ph, benzyl,4-cyano-3-trifluoromethylanilino; Y = leaving group and X = H; or X and Y are joined together to form a 3- to 6-membered heterocyclic ring, in particular oxirane ring; or X and A are joined together to form a 5- to 10-membered fused or unfused heterocyclic ring with the proviso that if a ring nitrogen is present, it may be substituted by a 3-trifluoromethyl-4-cyanophenyl group), YCH2CMe:CH2 (Y = same as above), or YCH2COMe (Y = same as above). Thus, 0.500 g N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-2-oxiranecarboxamide (III) was dissolved in dissolved in a mixture of 40 mL CHCl3 and 40 mL H2O, successively treated with 371 mg sodium p-fluorobenzenesulfinate and 298 mg tetrabutylammonium bromide, and refluxed for 96 h to give, after workup and silica gel chromatog., 380 mg I (48% yield). Similarly, chiral (R)-I was obtained using chiral epoxide (S)-III in 43% yield.

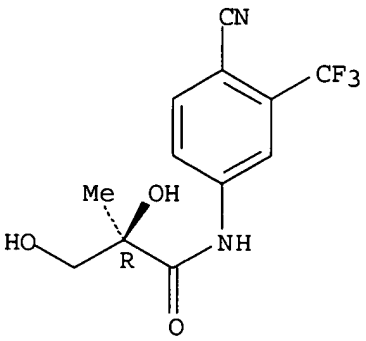
IT **316373-92-9P**, N-[4-Cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methylpropanamide **316373-93-0P**, N-[4-Cyano-3-(trifluoromethyl)phenyl]-(2R)-2,3-dihydroxy-2-methylpropanamide **316373-94-1P**, (2S)-N-[4-Cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methylpropanamide
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of bicalutamide by coupling of N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-2-orixanecarboxamide or -3-(halo or mesyloxy)-2-hydroxy-2-methylpropanamide with sodium p-fluorobenzenesulfinate)

RN 316373-92-9 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-(9CI) (CA INDEX NAME)



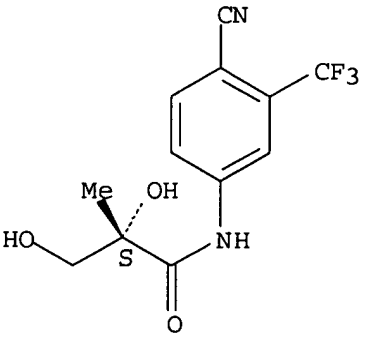
RN 316373-93-0 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



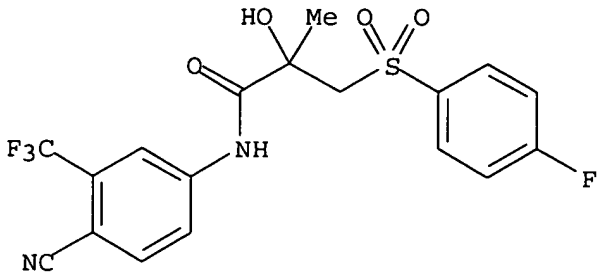
RN 316373-94-1 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



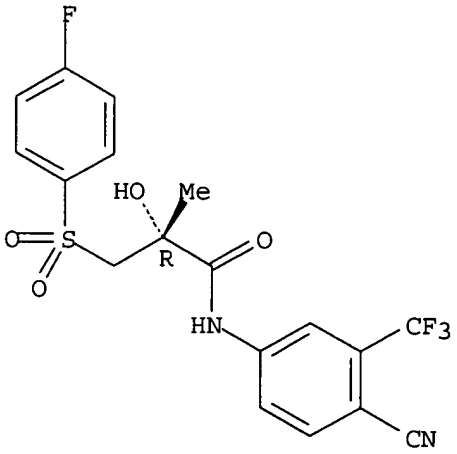
IT **90357-06-5P**, Bicalutamide **113299-40-4P**, (R)-Bicalutamide
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of bicalutamide by coupling of N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-2-orixanecarboxamide or -3-(halo or mesyloxy)-2-hydroxy-2-methylpropanamide with sodium p-fluorobenzenesulfinate)

RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)




RN 113299-40-4 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




L12 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:511288 HCAPLUS
DOCUMENT NUMBER: 139:85122
TITLE: Process for preparing bicalutamide and crystals thereof
INVENTOR(S): Shintaku, Tetsuya; Katsura, Tadashi; Itaya, Nobushige
PATENT ASSIGNEE(S): Sumika Fine Chemicals Co., Ltd., Japan
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003053920 | A1 | 20030703 | WO 2002-JP13058 | 20021213 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

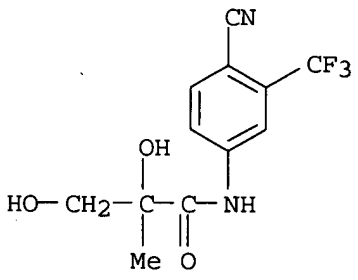
| | | | | | |
|---|---|---|---|---|---|
| CA 2469594 | AA | 20030703 | CA 2002-2469594 | | 20021213 |
| AU 2002354475 | A1 | 20030709 | AU 2002-354475 | | 20021213 |
| EP 1462442 | A1 | 20040929 | EP 2002-788815 | | 20021213 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | | |
| BR 2002014933 | A | 20041214 | BR 2002-14933 | | 20021213 |
| US 2003191337 | A1 | 20031009 | US 2003-362410 | | 20030224 |
| US 6740770 | B2 | 20040525 | | | |
| US 2004133031 | A1 | 20040708 | US 2003-740140 | | 20031218 |
| ZA 2004004891 | A | 20050621 | ZA 2004-4891 | | 20040621 |
| PRIORITY APPLN. INFO.: | | | JP 2001-380686 | A | 20011213 |
| | | | JP 2002-166213 | A | 20020606 |
| | | | WO 2002-JP13058 | W | 20021213 |
| | | | US 2003-362410 | A3 | 20030224 |

AB The invention relates to crystals of bicalutamide having a specific crystal form, and industrially practicable processes for the production of bicalutamide and crystals thereof; these processes are excellent in environmental friendliness and economical efficiency. Bicalutamide was prepared by epoxidn. of N-methacryloyl-4-cyano-3-trifluoromethylaniline, followed by reaction with 4-fluorothiophenol, and oxidation

IT **316373-92-9P**
RL: BYP (Byproduct); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(preparation of bicalutamide in multi-step process starting from N-methacryloyl-4-cyano-3-trifluoromethylaniline and process for production of crystals of bicalutamide)

RN 316373-92-9 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl- (9CI) (CA INDEX NAME)

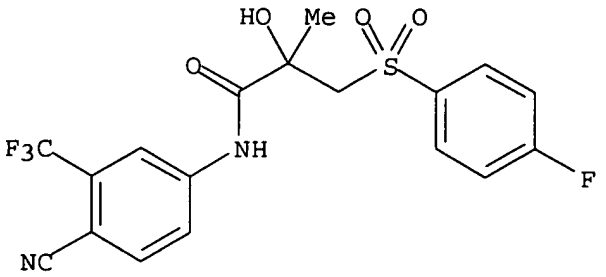



IT **90357-06-5P**, Bicalutamide
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of bicalutamide in multi-step process starting from

N-methacryloyl-4-cyano-3-trifluoromethylaniline and process for production of crystals of bicalutamide)

RN 90357-06-5 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:300625 HCAPLUS

DOCUMENT NUMBER: 138:321017

TITLE: Process for making bicalutamide using a p-fluorobenzenesulfinic acid salt.

INVENTOR(S): Thijs, Lambertus; Keltjens, Rolf; Ettema, Gerrit Jan Bouke

PATENT ASSIGNEE(S): Synthon B.V., Neth.

SOURCE: U.S. Pat. Appl. Publ., 24 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003073742 | A1 | 20030417 | US 2002-261492 | 20021002 |
| US 6818766 | B2 | 20041116 | | |
| WO 2004031136 | A1 | 20040415 | WO 2003-EP11166 | 20031001 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003273965 | A1 | 20040423 | AU 2003-273965 | 20031001 |
| EP 1546093 | A1 | 20050629 | EP 2003-757932 | 20031001 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| US 2004068135 | A1 | 20040408 | US 2003-682530 | 20031010 |
| PRIORITY APPLN. INFO.: | | | US 2002-261492 A | 20021002 |
| | | | WO 2003-EP11166 W | 20031001 |

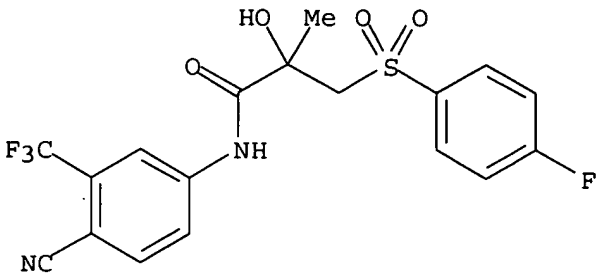
OTHER SOURCE(S): CASREACT 138:321017; MARPAT 138:321017

AB Title process is claimed. Thus, N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-2-oxiranecarboxamide (preparation given), Na p-fluorobenzenesulfinate, and Bu4NBr were refluxed together for 96 h to give 48% bicalutamide.

IT **90357-06-5P**, Bicalutamide **113299-40-4P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(process for making bicalutamide using a p-fluorobenzenesulfinic acid salt)

RN 90357-06-5 HCAPLUS

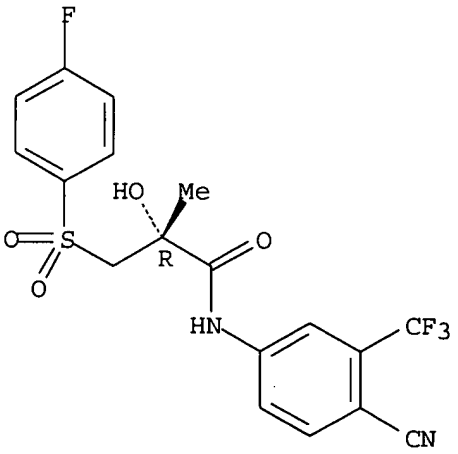
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)




RN 113299-40-4 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

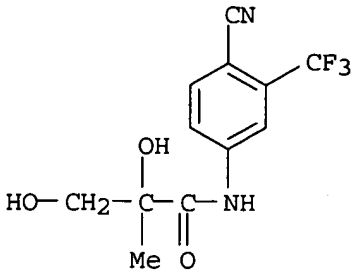
Absolute stereochemistry. Rotation (-).




IT **316373-92-9P 316373-93-0P 316373-94-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for making bicalutamide using a p-fluorobenzenesulfinic acid salt)

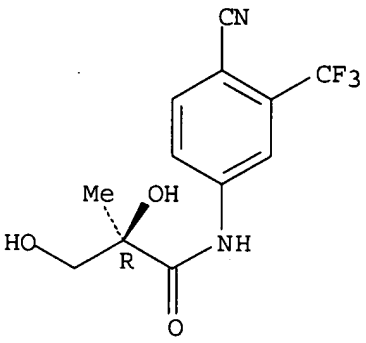
RN 316373-92-9 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl- (9CI) (CA INDEX NAME)



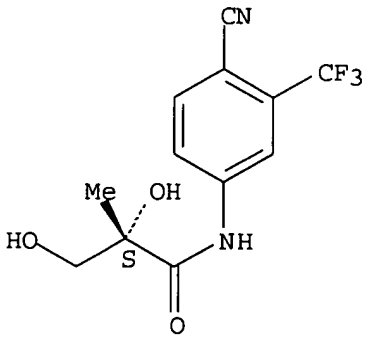
RN 316373-93-0 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 316373-94-1 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:12441 HCAPLUS
DOCUMENT NUMBER: 134:86040

TITLE: Preparation of bicalutamide enantiomers
INVENTOR(S): Soros, Bela; Tuba, Zoltan; Galik, Gyorgy; Bor, Adam; Demeter, Adam; Trischler, Ferenc; Horvath, Janos; Balaik, Janos
PATENT ASSIGNEE(S): Richter Gedeon Vegyeszeti Gyar Rt., Hung.
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001000608 | A1 | 20010104 | WO 2000-HU49 | 20000526 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1189898 | A1 | 20020327 | EP 2000-937111 | 20000526 |
| EP 1189898 | B1 | 20030312 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| AT 234294 | E | 20030315 | AT 2000-937111 | 20000526 |
| ES 2188550 | T3 | 20030701 | ES 2000-937111 | 20000526 |
| PRIORITY APPLN. INFO.: | | | HU 1999-1937 A | 19990610 |
| | | | WO 2000-HU49 W | 20000526 |

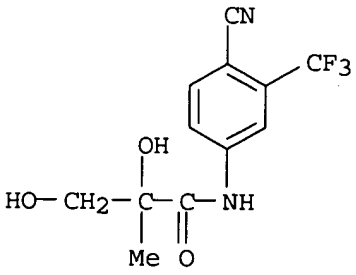
OTHER SOURCE(S): CASREACT 134:86040

AB Racemic HOCH2CMe(OH)CO2H was optically resolved and the enantiomers treated with SOCL2 to give the dioxothiolanonecarbonyl chloride which was amidated by H2NC6H3(CF3)(CN)-3,4. The deprotected dihydroxyamide was O-acylated by RSO2Cl (R = 4-Me- or -BrC6H4) and the product thioetherified by 4-FC6H4SNa to give, after oxidation, the title compds.

IT **316373-92-9P 316373-93-0P 316373-94-1P**
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of bicalutamide enantiomers)

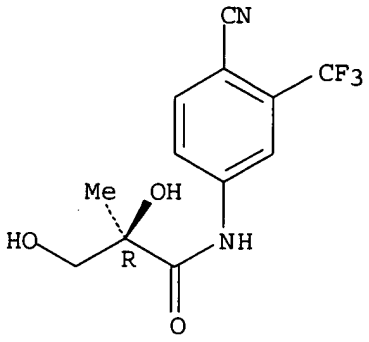
RN 316373-92-9 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-(9CI) (CA INDEX NAME)



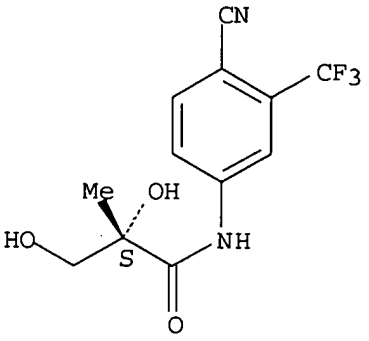
RN 316373-93-0 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

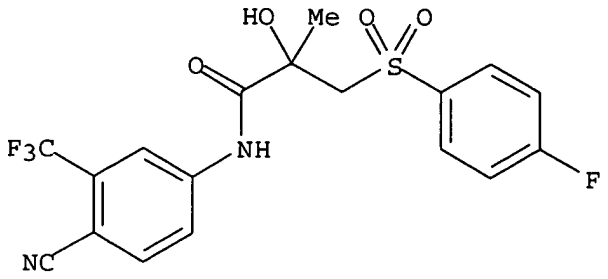



RN 316373-94-1 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

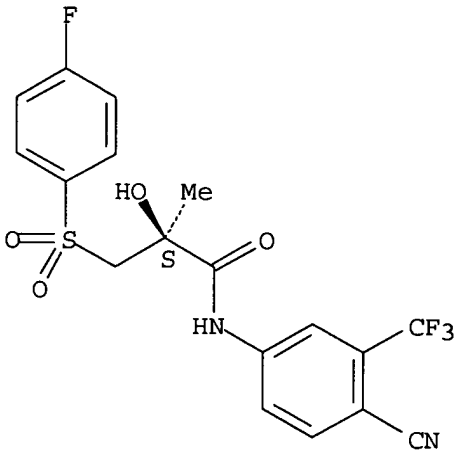



IT **90357-06-5P 113299-38-0P 113299-40-4P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of bicalutamide enantiomers)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



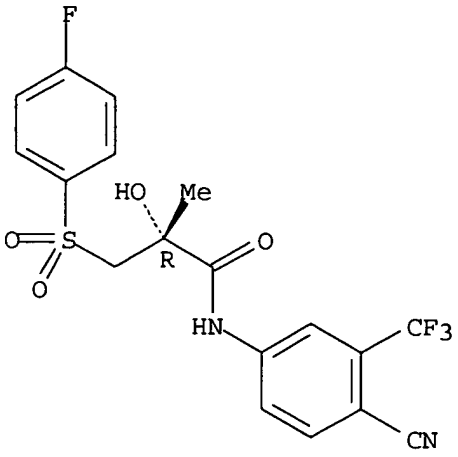
RN 113299-38-0 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 113299-40-4 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

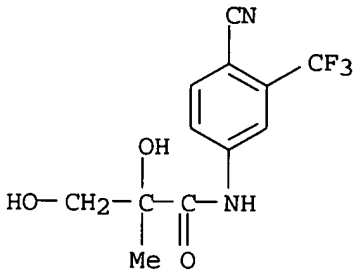


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l11 ibib abs hitstr tot

L11 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1274892 HCAPLUS
DOCUMENT NUMBER: 144:199095
TITLE: High-performance liquid chromatographic enantioseparation of bicalutamide and its related compounds
AUTHOR(S): Toeroek, Roland; Bor, Adam; Orosz, Gyoergy; Lukacs, Ferenc; Armstrong, Daniel W.; Peter, Antal
CORPORATE SOURCE: Department of Inorganic and Analytical Chemistry, University of Szeged, Szeged, H-6720, Hung.
SOURCE: Journal of Chromatography, A (2005), 1098(1-2), 75-81
CODEN: JCRAEY; ISSN: 0021-9673
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Direct high-performance liquid chromatog. methods were developed for the enantiosepn. of (R,S)-bicalutamide (1) and its analogs (±)-3-chloro-N-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropanamide (2), (±)-N-(4-cyano-3-(trifluoro-methyl)phenyl)-2-methyloxirane-2-carboxamide (3), (±)-4-fluorophenylsulfonyl-2-hydroxy-2-methylpropionic acid (4), and (±)-3-hydroxy-N-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropanamide (5). The methods involved the use of a cellulose-based Chiralcel OD-H, macrocyclic glycopeptide-based Chirobiotic T, TAG and R, β-cyclodextrin-based Cyclobond I 2000SN, and t-Bu carbamate-derivatized quinine-based columns. The conditions affording the best resolution were found by selection and variation of the mobile-phase compns., and the differences in separation capability of the methods were noted. The sequence of elution of the enantiomers was determined in all cases.
IT **316373-92-9**
RL: ANT (Analyte); ANST (Analytical study)
(HPLC enantiosepn. of bicalutamide and its related compds.)
RN 316373-92-9 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-

(9CI) (CA INDEX NAME)

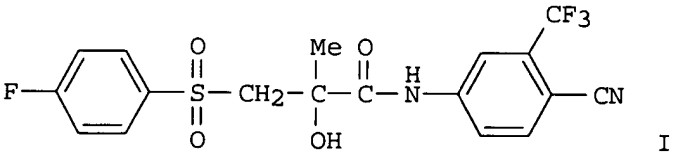


REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

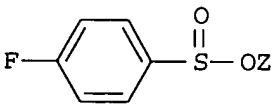
L11 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:293441 HCAPLUS
DOCUMENT NUMBER: 140:303414
TITLE: Process for making bicalutamide and intermediates thereof
INVENTOR(S): Thijs, Lambertus; Keltjens, Rolf; Ettema, Gerrit J. B.
PATENT ASSIGNEE(S): Neth.
SOURCE: U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S. Ser. No. 261,492.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2004068135 | A1 | 20040408 | US 2003-682530 | 20031010 |
| US 2003073742 | A1 | 20030417 | US 2002-261492 | 20021002 |
| US 6818766 | B2 | 20041116 | | |

PRIORITY APPLN. INFO.: US 2002-261492 A2 20021002
OTHER SOURCE(S): MARPAT 140:303414
GI



I



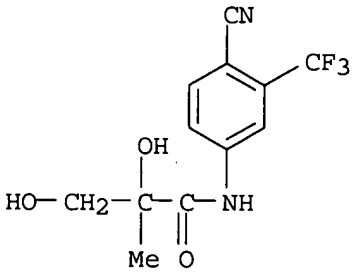
II

AB Bicalutamide (I) and/or its intermediates are made by reaction of p-fluorobenzenesulfinic acid salt (II; Z = a cation) with

2-hydroxyisobutyric acid derivs. of formula YCH2C(Me)(OX)COA (A = OR; wherein R = H, C1-6 alkyl, C3-6 cycloalkyl, Ph, benzyl,4-cyano-3-trifluoromethylanilino; Y = leaving group and X = H; or X and Y are joined together to form a 3- to 6-membered heterocyclic ring, in particular oxirane ring; or X and A are joined together to form a 5- to 10-membered fused or unfused heterocyclic ring with the proviso that if a ring nitrogen is present, it may be substituted by a 3-trifluoromethyl-4-cyanophenyl group), YCH2CMe:CH2 (Y = same as above), or YCH2COMe (Y = same as above). Thus, 0.500 g N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-2-oxiranecarboxamide (III) was dissolved in dissolved in a mixture of 40 mL CHCl3 and 40 mL H2O, successively treated with 371 mg sodium p-fluorobenzenesulfinate and 298 mg tetrabutylammonium bromide, and refluxed for 96 h to give, after workup and silica gel chromatog., 380 mg I (48% yield). Similarly, chiral (R)-I was obtained using chiral epoxide (S)-III in 43% yield.

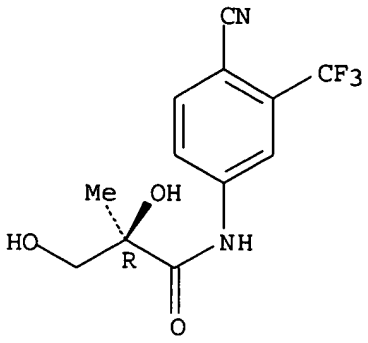
IT **316373-92-9P**, N-[4-Cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methylpropanamide **316373-93-0P**, N-[4-Cyano-3-(trifluoromethyl)phenyl]-(2R)-2,3-dihydroxy-2-methylpropanamide **316373-94-1P**, (2S)-N-[4-Cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methylpropanamide
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of bicalutamide by coupling of N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-2-orixanecarboxamide or -3-(halo or mesyloxy)-2-hydroxy-2-methylpropanamide with sodium p-fluorobenzenesulfinate)

RN 316373-92-9 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl- (9CI) (CA INDEX NAME)



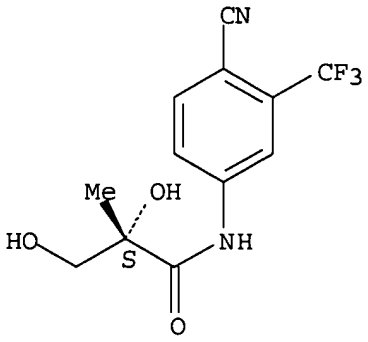

RN 316373-93-0 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RN 316373-94-1 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).




L11 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:511288 HCAPLUS
DOCUMENT NUMBER: 139:85122
TITLE: Process for preparing bicalutamide and crystals thereof
INVENTOR(S): Shintaku, Tetsuya; Katsura, Tadashi; Itaya, Nobushige
PATENT ASSIGNEE(S): Sumika Fine Chemicals Co., Ltd., Japan
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003053920 | A1 | 20030703 | WO 2002-JP13058 | 20021213 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

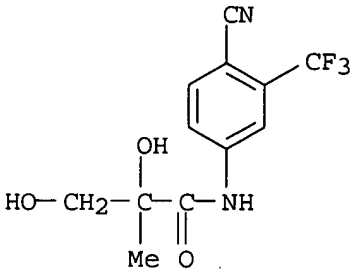
| | | | | |
|---|---|---|---|---|
| CA 2469594 | AA | 20030703 | CA 2002-2469594 | 20021213 |
| AU 2002354475 | A1 | 20030709 | AU 2002-354475 | 20021213 |
| EP 1462442 | A1 | 20040929 | EP 2002-788815 | 20021213 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| BR 2002014933 | A | 20041214 | BR 2002-14933 | 20021213 |
| US 2003191337 | A1 | 20031009 | US 2003-362410 | 20030224 |
| US 6740770 | B2 | 20040525 | | |
| US 2004133031 | A1 | 20040708 | US 2003-740140 | 20031218 |
| ZA 2004004891 | A | 20050621 | ZA 2004-4891 | 20040621 |
| PRIORITY APPLN. INFO.: | | | JP 2001-380686 A | 20011213 |
| | | | JP 2002-166213 A | 20020606 |
| | | | WO 2002-JP13058 W | 20021213 |
| | | | US 2003-362410 A3 | 20030224 |

AB The invention relates to crystals of bicalutamide having a specific crystal form, and industrially practicable processes for the production of bicalutamide and crystals thereof; these processes are excellent in environmental friendliness and economical efficiency. Bicalutamide was prepared by epoxidn. of N-methacryloyl-4-cyano-3-trifluoromethylaniline, followed by reaction with 4-fluorothiophenol, and oxidation

IT **316373-92-9P**
RL: BYP (Byproduct); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(preparation of bicalutamide in multi-step process starting from N-methacryloyl-4-cyano-3-trifluoromethylaniline and process for production of crystals of bicalutamide)

RN 316373-92-9 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:300625 HCAPLUS

DOCUMENT NUMBER: 138:321017

TITLE: Process for making bicalutamide using a p-fluorobenzenesulfinic acid salt.

INVENTOR(S): Thijs, Lambertus; Keltjens, Rolf; Ettema, Gerrit Jan Bouke

PATENT ASSIGNEE(S): Synthon B.V., Neth.

SOURCE: U.S. Pat. Appl. Publ., 24 pp.

CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

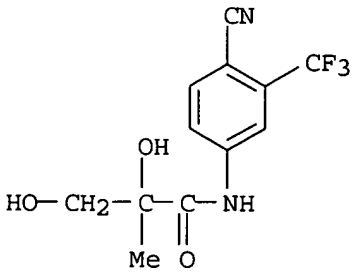
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003073742 | A1 | 20030417 | US 2002-261492 | 20021002 |
| US 6818766 | B2 | 20041116 | | |
| WO 2004031136 | A1 | 20040415 | WO 2003-EP11166 | 20031001 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003273965 | A1 | 20040423 | AU 2003-273965 | 20031001 |
| EP 1546093 | A1 | 20050629 | EP 2003-757932 | 20031001 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| US 2004068135 | A1 | 20040408 | US 2003-682530 | 20031010 |
| PRIORITY APPLN. INFO.: | | | US 2002-261492 A | 20021002 |
| | | | WO 2003-EP11166 W | 20031001 |

OTHER SOURCE(S): CASREACT 138:321017; MARPAT 138:321017

AB Title process is claimed. Thus, N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-2-oxiranecarboxamide (preparation given), Na p-fluorobenzenesulfinate, and Bu4NBr were refluxed together for 96 h to give 48% bicalutamide.

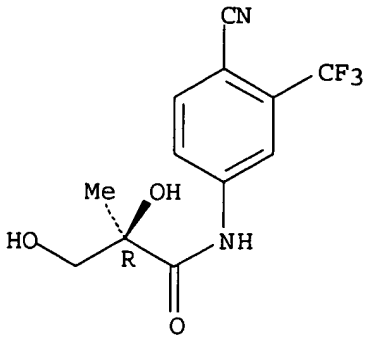
IT **316373-92-9P 316373-93-0P 316373-94-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for making bicalutamide using a p-fluorobenzenesulfinic acid salt)

RN 316373-92-9 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl- (9CI) (CA INDEX NAME)



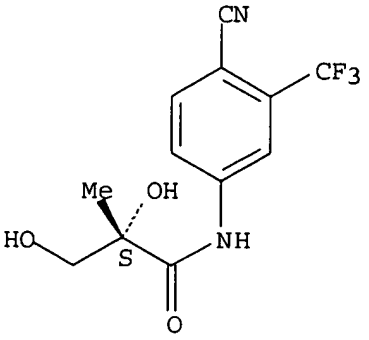

RN 316373-93-0 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 316373-94-1 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:12441 HCAPLUS
DOCUMENT NUMBER: 134:86040
TITLE: Preparation of bicalutamide enantiomers
INVENTOR(S): Soros, Bela; Tuba, Zoltan; Galik, Gyorgy; Bor, Adam; Demeter, Adam; Trischler, Ferenc; Horvath, Janos; Brlik, Janos
PATENT ASSIGNEE(S): Richter Gedeon Vegyeszeti Gyar Rt., Hung.
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001000608 | A1 | 20010104 | WO 2000-HU49 | 20000526 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,

LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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|---|---|---|---|---|---|
| EP 1189898 | A1 | 20020327 | EP 2000-937111 | | 20000526 |
| EP 1189898 | B1 | 20030312 | | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | | |
| AT 234294 | E | 20030315 | AT 2000-937111 | | 20000526 |
| ES 2188550 | T3 | 20030701 | ES 2000-937111 | | 20000526 |
| PRIORITY APPLN. INFO.: | | | HU 1999-1937 | A | 19990610 |
| | | | WO 2000-HU49 | W | 20000526 |

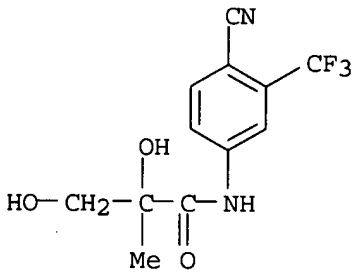
OTHER SOURCE(S): CASREACT 134:86040

AB Racemic HOCH2CMe(OH)CO2H was optically resolved and the enantiomers treated with SOCL2 to give the dioxothiolanonecarbonyl chloride which was amidated by H2NC6H3(CF3)(CN)-3,4. The deprotected dihydroxyamide was O-acylated by RSO2Cl (R = 4-Me- or -BrC6H4) and the product thioetherified by 4-FC6H4SNa to give, after oxidation, the title compds.

IT **316373-92-9P 316373-93-0P 316373-94-1P**
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of bicalutamide enantiomers)

RN 316373-92-9 HCAPLUS

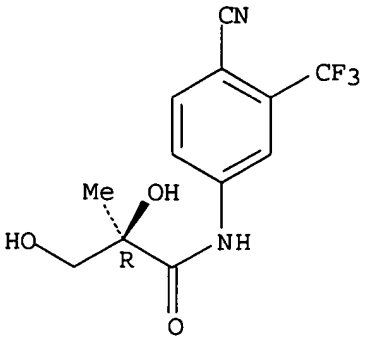
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl- (9CI) (CA INDEX NAME)




RN 316373-93-0 HCAPLUS

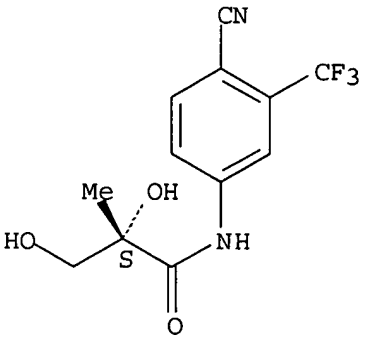
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).




RN 316373-94-1 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-2,3-dihydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).




REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 74.02 | 469.08 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -9.75 | -13.50 |

STN INTERNATIONAL LOGOFF AT 12:33:01 ON 23 APR 2006